Cr^{3+}-Mediated Addition of Arylzincs to Aldehydes

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Addition of arylzincs to aldehydes was achieved by making use of the novel transmetallation of arylzincs into Cr^{3+} compounds. Various α-substituted benzyl alcohols or 3-substituted 1(3*H*)-isobenzofuranones, containing reactive functional groups, were synthesized in good yields. Me_3SiCl exerted beneficial effects on the reaction.

As synthetic reagents providing carbon-nucleophiles, organozincs surpass common organometallics like organolithiums or Grignard reagents in chemoselectivity. This comes from the fact that the reactivity of organozincs is too low to react with electrophilic functional groups like ester, nitrile, amide, or halogen. Thus, such functional groups can be incorporated even into organozincs themselves.[1] Meanwhile, several ways have been invented to increase the reactivity of organozincs. Hence, functionalized organozincs have become indispensable reagents for the synthesis of polyfunctional molecules.[2] In the course of our study on the synthesis and synthetic application of functionalized arylzincs,[3] we investigated into the reaction of the arylzincs with aldehydes. We intended to overcome the inertness of arylzincs towards aldehydes by the novel transmetallation of organozincs into Cr^{3+} compounds.[4]

1,1,3,3-Tetramethylurea (TMU) solution of arylzinc **1a**[5] was treated with $CrCl_3$ (1 equiv.) at room temperature under N_2 first. $CrCl_3$ (rose color solid) dissolved gradually to be a green solution after 3.5 h stirring. Propanal **2a** (1 equiv.) was added to the solution and stirring was continued over night to yield 1(3*H*)-isobenzo-furanone **3a** in a yield of 82% . A small amount of dimethyl 2, 2'-biphenyldicarboxylate was also yielded (3%). It is to be noted that **3a** was obtained not at all when three components of **1a**, **2a**, and $CrCl_3$ were mixed together without the pre-treatment of **1a** with $CrCl_3$. In this case, methyl benzoate was obtained in a quantitative yield. These results probably indicate that an arylchromium intermediate was really formed from **1a** and $CrCl_3$, which was reactive enough to couple with a carbonyl group of **2a** and formed **3a** ultimately.[6,7] In a similar manner as above, various alkylaldehydes or alkenylaldehyde were successfully reacted with an arylchromium intermediate derived from **1a** to yield the corresponding 1(3*H*)-isobenzofuranones in good yields as shown in Table 1.

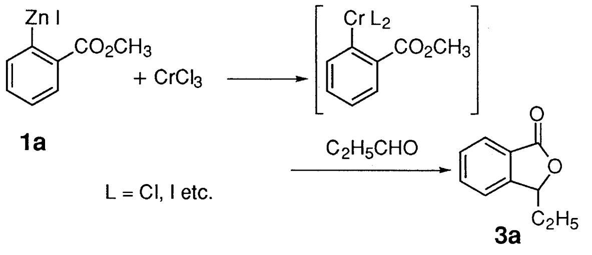
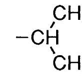
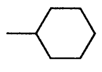
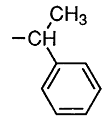
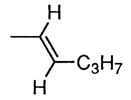
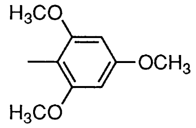
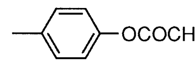
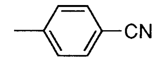
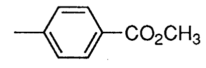
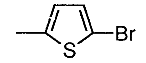
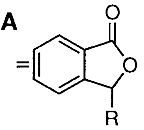


Table 1. Synthesis of 1(3*H*)-isobenzofuranones[a]

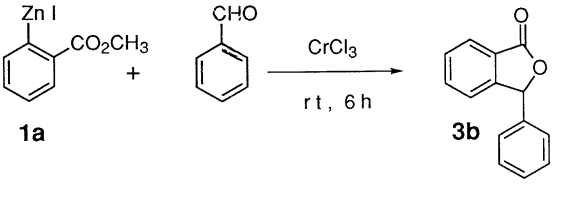
Run	Aldehyde R-CHO R	Product **A**[b] Yield / %[c]
1	 $-CH(CH_3)CH_3$	77
2		73
3		81[d]
4		66
5		83
6		63
7		68
8		78
9		73

[a] The reaction was carried out as described in the text.

[b] **A**  [c] Isolated Yield.

[d] The ratio of diastereomers was about 1.

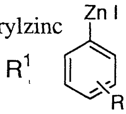
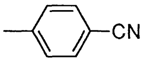
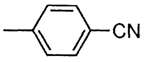
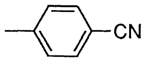
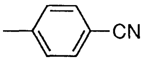
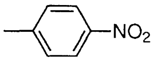
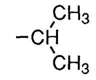
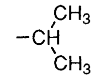
For the reaction of **1a** with nonenolizable arylaldehydes, pre-treatment of **1a** with $CrCl_3$ was not necessarily an essential process. Thus, for example, addition of **1a** to benzaldehyde took place readily at room temperature in the presence of $CrCl_3$ (1 equiv.) to afford the corresponding 1(3*H*)-isobenzofuranone **3b** in a yield of 78%. A catalytic amount of $CrCl_3$ (0.25 equiv.) was sufficient for the reaction but took longer to reach to the end



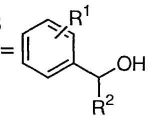
(70 h) . Neither electron-donating groups nor electron-withdrawing groups attached to aromatic rings of arylaldehydes interfered with the reaction between **1a** and aldehydes in the presence of $CrCl_3$. The results are also summarized in Table 1.

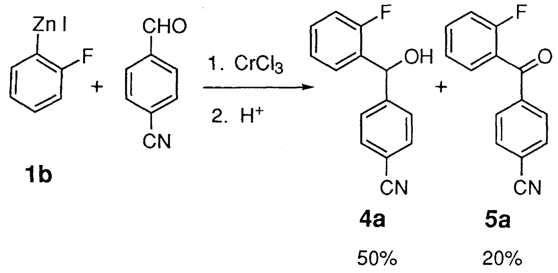
Reactions of functionalized arylzincs like **1b-g** with aldehydes were tried next, according to the procedures developed above. Addition reaction took place, in fact, but suffered from side reactions. That is, in the reaction of arylzincs with alkylaldehydes, organometallic species underwent the protonolysis appreciably even if aldehydes were added to arylchromium intermediates prepared previously from arylzincs and $CrCl_3$. Whereas, in the reaction of such arylzinc with arylaldehyde, a portion of the adduct (alkoxychromium compound) reacted further to yield ketone. For example, the reaction of arylzinc **1b** with *p*-cyanobenzaldehyde mediated by $CrCl_3$ gave the desired diaryl carbinol **4a** along with ketone **5a**. However,these problems were solved by the addition of Me_3SiCl to the reaction systems.[8] Thus, in the presence of Me_3SiCl, the reactions (between arylzincs, $CrCl_3$, and alkylaldehydes via arylchromium intermediates or arylzincs, $CrCl_3$, and aryl-aldehydes) gave α-substituted benzyl alcohols in good yields. The results are summarized in Table 2.

Table 2. Synthesis of benzyl alcohols[a]

Run	Arylzinc 	Aldehyde R^2-CHO R^2	Product B[b] Yield / %[c]
10	2-F **1b**		81
11	3-Cl **1c**		81
12	3-CO_2CH_3 **1d**		82
13	4-CO_2CH_3 **1e**		81
14	4-Br **1f**		81
15	3-Br **1g**	$-CH_2CH_3$	68
16	**1g**	 $-CH(CH_3)_2$	62
17	**1d**	 $-CH(CH_3)_2$	72

[a] The reaction was carried out as described in the text.

[b] B =  [c] Isolated yield.



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References and Notes

1 P. Knochel, in "Comprehensive Organometallic Chemistry II," ed by A. McKillop, Pergamon Press, Oxford (1995), Vol. 11, p. 159.

2 P. Knochel and R. D. Singer, *Chem. Rev.*, **93**, 2117 (1993); E. Erdik, *Tetrahedron*, **48**, 9577 (1992).

3 K. Takagi, *Chem. Lett.*, **1993**, 469; K. Takagi, Y. Shimoishi, and K. Sasaki, *Chem. Lett.*, **1994**, 2055.

4 Generally, arylzinc halides are less reactive than diarylzincs, dialkylzincs, or alkylzinc halides. There was no efficient way to bring about the addition of arylzinc halides to aldehydes. For the addition of R_2Zn, Ar_2Zn, or RZnX to aldehydes, see: K. Soai and S. Niwa, *Chem. Rew.*, **92**, 833 (1992); H. Ochiai, T. Nishihara, Y. Tamaru, and Z. Yoshida, *J. Org. Chem.*, **53**, 1343 (1988); Y. Kondo, N. Takazawa, C. Yamazaki, and T. Sakamoto, *J. Org. Chem.*, **59**, 4717 (1994); F. Hong, X. Tang, and C. Hu, *J. Chem. Soc., Chem. Commun.*, **1994**, 289.

5 Arylzincs, used in this study, were prepared by the reaction of aryl iodides with zinc powder in TMU solvent under the irradiation of ultrasound. For the procedure, see Ref. 3.

6 For other Cr^{3+}-mediated addition of organometallics to aldehydes, see: N. A. Saccomano, "Comprehensive Organic Synthesis," ed by B. M. Trost, Pergamon Press, Oxford (1991), Vol. 1, p. 173; T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **35**, 386 (1996).

7 $CrCl_2$-mediated reaction of aryl halides with aldehydes is known, which needs the use of hygroscopic and oxidizable Cr(II) in a huge excess, see: K. Takai, K. Kimura, T. Kuroda, T. Hiyama, and H. Nozaki, *Tetrahedron Lett.*, **24**, 5281 (1983); K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, and H. Nozaki, *J. Am. Chem. Soc.*, **108**, 6048 (1986).

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